**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| Appellant: | Monty Krieger | | |
| Serial No.: | 09/148,012 | Art Unit: | 1647 |
| Filed: | September 4, 1998 | Examiner: | Robert S. Landsman |

For: *SR-BI ANTAGONIST AND USE THEREOF AS CONTRACEPTIVES AND IN THE TREATMENT OF STEROIDAL OVERPRODUCTION*

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**APPEAL BRIEF**

Sir:

This is an appeal from the final rejection of claims 1-10, 12, 15, 16, and 19-22 in the Office Action mailed August 15, 2005, in the above-identified patent application. A Notice of Appeal was mailed on November 15, 2005. Submitted with this Amendment and Response is a Petition for Extension of Time, along with the required fee for a small entity, to extend the period for response four months, to and including May 15, 2006. The Commissioner is hereby authorized to charge $250.00, the fee for the filing of this Appeal Brief for a small entity and $795.00, the fee for filing the Petition for Extension of Time for a small entity, to Deposit Account No. 50-3129. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

## (1) REAL PARTY IN INTEREST

The real party in interest of this application is Massachusetts Institute of Technology, the assignee, and the inventor Monty Krieger.

## (2) RELATED APPEALS AND INTERFERENCES

This case was previously on appeal as Appeal No. 2004-1823 and remanded. There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

## (3) STATUS OF CLAIMS ON APPEAL

Claims 1-9, 12, 15, 16, and 19-22 are pending and on appeal. Claim 19 is withdrawn. Claims 10, 11, 13, 14, 17 and 18 have been canceled. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

## (4) STATUS OF AMENDMENTS

An amendment after final rejection was filed via facsimile transmission on January 17, 2006. In the Advisory Action mailed three months later, after multiple calls, on April 10, 2006, the Examiner indicated that this amendment would be entered. An appendix sets forth the claims on appeal.

## (5) SUMMARY OF THE INVENTION

Claim 1 defines a method for inhibiting pregnancy or decreasing production of steroids in a mammal comprising administering a compound inhibiting uptake, binding or transport of

cholesteryl ester by SR-BI in the mammal in an amount effective to inhibit pregnancy or to decrease production of steroids in disorders involving steroidal overproduction. Claim 8 defines the method wherein the mammal is a female and the compound is administered in an amount effective to prevent normal reproductive function (i.e., prevent pregnancy). Claim 9 defines the method wherein the mammal has a disorder characterized by an overproduction of steroids. Claim 12 define the method of claim 1 wherein the mammal has a disorder which can be treated by decreasing production of steroids. (see page 7, line 19-page 8, lines 5; page 13, lines 19-20; paragraph bridging pages 10 and 11; and lines 15-20, bridging pages 12 and 13).

Claim 2 restricts the compound to one altering (decreasing or increasing) SR-BI expression in a tissue (page 10, lines 19-27). Claim 4 is specific to decreasing SR-BI expression in the tissue of the mammal; Claim 5 is specific to increasing SR-BI expression in the tissue of the mammal. Claim 3 defines the compound as altering (decreasing or increasing) binding of SR-BI to high density lipoprotein including cholesteryl ester or other lipoproteins (page 12, lines 16-18; Example 2). Claim 6 is specific to decreasing SR-BI binding to lipoprotein or transfer of cholesteryl ester in the tissue of the mammal. Claim 7 is specific to increasing SR-BI binding to lipoprotein or transfer of cholesteryl ester in the tissue of the mammal.

Claim 15 defines the method of claim 1 wherein the compound differentially alters the activity of, or expression of, SR-BI in different tissues; claim 16 defines the compound as increasing SR-BI expression in reproductive tissues and decreasing or not increasing SR-BI expression in liver (page 12, lines 25-26; page 13, lines 14-15; page 13, lines 23-25; and lines 19-20 bridging pages 10-11).

Claim19, which has been withdrawn as directed to a non-elected species, defines the compound as an antibody to SR-BI (page 12, lines 24-28). Claim 20 defines the compound as a drug that decreases production of steroids via selective binding to SR-BI (page 11, lines 10-17). Claim 21 defines the compound as decreasing cholesterol levels to decrease steroid levels (page 12, lines 26-28); claim 22 limits this to a compound which inhibits cholesterol transport.

**(6) ISSUES ON APPEAL**

The issues presented on appeal are:

(1) whether claims 1-10, 12, 15, 16, and 20-22 are enabled as required by 35 U.S.C. § 112, first paragraph; and

(2) whether claims 1-10, 12, 15, 16, and 20-22 comply with the written description as required by 35 U.S.C. § 112, first paragraph.

**(7) GROUPING OF CLAIMS**

The claims do not stand or fall together, as discussed below.

**(8) ARGUMENTS**

**(a) The Claimed Invention**

Appellant was the first to recognize that lipoprotein and/or cholesterol levels affect a female's ability to reproduce. Appellant was the first to recognize that SR-BI, by virtue of its role as the only known transporter of cholesterol, which is critical to steroid production, plays a major role in female reproduction. Appellant demonstrated the criticality of SR-BI, and its role on lipoprotein and cholesterol levels, using SR-BI knockout mice. The homozygous knockout

females are unable to carry a fetus to term. Heterozygotes are able to do so. These studies are described in the patent application as filed.

The data presented in the specification clearly demonstrate that multiple compounds have been identified and are representative of widely disparate species, ranging from nucleic acid molecules encoding SR-BI to organic compounds for lowering cholesterol.

In example 5, Appellant demonstrated that transient increases in SR-BI expression following administration of an adenoviral vector encoding SR-BI results in a decrease in cholesterol levels. In example 6, the Appellant demonstrated that SR-BI knockout animals exhibit the opposite phenotype; increased cholesterol levels (see Table 3). Data in example 7 further shows that these animals are also infertile. Antibody blocking studies have also showed similar results using antibodies to block cholesterol transport, resulting in lowered cholesterol levels, as described in Example 8, page 55.

The reagents and methods provided in the present specification were used to subsequently show the restoration of fertility in an SR-BI knockout mouse (or their transplanted oocytes) in the absence of ovarian and/or extraovarian SR-BI expression by manipulations that modify the structure, composition and/or abundance of their abnormal plasma lipoproteins. These manipulations centered on administration of probucol, a cholesterol lowering drug (Meittinen, *et al*., *J. Clin. Invest*. 108:1717-1722 (2001) submitted with the Amendment and Response filed February 15, 2002, a copy of which is enclosed in the Evidence Appendix).

The application therefore describes to one skilled in the art that SR-BI is essential for normal female fertility; that decreasing levels of SR-BI activity decreases cholesterol levels and

alters lipoprotein levels; and that restoring SR-BI activity normalized cholesterol levels and lipoprotein profiles, with a concurrent increase in steroidogenesis and female fertility. The application further teaches that one can use any number of compounds to alter SR-BI levels: viral vectors to increase SR-BI expression; antibodies to block SR-BI activity and concurrent transport of cholesterol; and organic molecules identified by routine screening assays using SR-BI binding and uptake studies. These compounds alter SR-BI activity either by increasing the amount of transport or by decreasing transport (for example, using viral vectors or antibodies).

The present application, and its analysis of SR-BI knockout mice, ties together fertility and cholesterol level. The direct correlation that exists between cholesterol/HDL and the existence of SR-BI, lies at the core of the claimed method. Many compounds that already exist for regulating cholesterol levels can be used to inhibit fertility (i.e. pregnancy) *via*, the inhibition of SR-BI expression or activity. The compounds can also be used to treat disorders characterized by elevated steroidal levels. It would not require undue experimentation to identify these known compounds, the patients to be treated, or what constitutes an effective amount. Moreover, one skilled in the art would have no difficulty in identifying the scope of the claimed method in view of the specification, the examples, and the knowledge available to those skilled in the art.

The articles submitted with the Amendment and Response filed January 17, 2006, copies of which are enclosed in the Evidence Appendix, establish that mouse models are accepted models for human gonadotropin signaling pathologies, and thus that the data appellant has provided with respect to the transgenic mice would be expected to be predictive of results in humans. See:

Burns and Matzuk, "Minireview: Genetic Models for the study of Gonadotropin Actions" Endocrinology 143(8):2823-2835 (2002)

Matzuk and Lomb, "Genetic dissection of mammalian fertility pathways" Nature Cell Biology & Nature Medicine Fertility Supplement (2002) online table.

**(b) Rejection Under 35 U.S.C. § 112, written description**

Claims 1-10, 12, 15, 16 and 20-22 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention.

***The Legal Standard for Written Description***

"There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed". *Wertheim*, 541 F.2d at 262, 191 USPQ at 96 (CCPA 1976). The written description requirement for a claimed genus may be satisfied through a sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or a disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the Appellant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus when there is substantial variation within

the genus, one must describe a sufficient variety of species to reflect the variation within the genus. On the other hand, there may be a situation where one species adequately supports a genus. See, e.g., *Rasmussen*, 650 F.2d at 1214, 211 USPQ at 326-27.

In the patent context, not all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if, in the knowledge of the art, the disclosed function is sufficiently correlated to a particular, known structure. (*Amgen v. Hoechst Marion Roussell* 314 F.3d 1313 Fed.Cir. 2003).

***The Specification Complies with the Written Description Requirement***

The claimed invention is based on the clear cut description of the nexus between fertility, steroidal levels and cholesterol levels. *The specification is replete with support for this novel connection* (see, for example, page 7, lines 21-22; page 13, lines 14-15; page 49, lines 16-20; page 49, lines 21-24 and Example 7). Because of this established connection, the appellant is claiming any compound that alters lipoprotein, LDL, HDL, or cholesterol levels mediated by SR-BI for the purpose of inhibiting pregnancy or decreasing production of steroids in a mammal. The examples in the specification clearly show that, for example, antibodies raised against a portion of the extracellular domain of the protein inhibit the selective uptake of HDL and delivery of HDL cholesterol to the steroidogenic pathway in cultured adrenal cells (Example 8, and in particular, Table 4, wherein anti-SR-BI inhibited the production of tritiated steroid derived from tritiated HDL). Adenoviral vectors encoding SR-BI (Example 5) are an additional example of a compound that has been shown to alter cholesterol levels (as will be discussed below in

more detail as it relates to enablement). In **each** of Examples 3, 5 and 8, the appellant has **reduced to practice a distinct compound** for altering cholesterol levels.

In Example 6, the SR-BI gene was inactivated in embryonic stem cells by standard recombination methods (strategy shown in Example 3). Blastocysts were injected with the embryonic stem cells, producing 24 male chimeric mice. F1 offspring (from crosses between the chimeric mice and wild type females) were either homozygous or heterozygous at the SR-BI locus. **F1 intercrosses generated F2 progeny, wherein the males were fertile and the homozygous females (-/- at the SR-BI locus) were unable to produce offspring (Example 7 further discusses the reproductive studies on these mice to make a determination regarding fertility)**. Example 6 then discusses the resultant elevated levels of plasma cholesterol in which the cholesterol and apolipoprotein profiles of the *heterozygous* mutants were similar to those of wild type controls, except that there was an increase in the amount of cholesterol in the HDL fractions. In the *F2 homozygous* mutant animals (-/- at the SR-BI locus), the cholesterol was found in a large, somewhat heterogeneous peak in the HDL range (*via* FPLC cholesterol analysis).

In view of the foregoing results (as discussed in detail in Example 6), one of ordinary skill in the art will readily recognize, not only the direct correlation that exists between cholesterol/HDL and the existence of SR-BI, but also the many compounds that already exist for regulating cholesterol levels. These compounds, well known for altering cholesterol levels, can be used to inhibit pregnancy or decrease steroidal overproduction via the modulation of SR-BI expression or activity. For further support in this regard, the Board's attention is again drawn to

the attachments to the Amendment filed August 13, 2002, the brochure for Alesse 28 tablets, attached in the Evidence Appendix.

The legal standard for written description does NOT require that the appellant reduce to practice all of the claimed species that may fall within the claimed genus. In this regard, the Board's attention is not only drawn to the three widely disparate types of compounds discussed in the foregoing paragraph, but additionally, and respectfully, drawn to the section in the specification entitled: "I. Inhibitors of SR-BI transport of cholesterol", and the section entitled: "II. Methods of Regulation of SR-BI cholesterol transport to alter steroidogenesis". The description clearly conveys that, in addition to the classes of compounds actually used to show reduction to practice, a number of other molecules were known and could be screened for utility in the claimed method.

The test under 35 U.S.C. 112 was clearly articulated by the Court in *Amgen Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.* 314 F.3d 1313, 65 USPQ 2d (Fed. Cir. 2003) as being different in the case where, as here, the reagents that could be used in a claimed method were known, and where one was claiming a novel class of compounds. The Court weighed heavily the fact that one was not claiming the class of compounds *per se*, but the use of the compounds. A different degree of description is required where compounds are known and one only needs to provide the criteria for their selection and use - a degree clearly met by appellant.

**(c) Rejection Under 35 U.S.C. § 112, enablement**

Claims 1-10, 12, 15, 16 and 20-22 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled for inhibiting pregnancy in any animal other than SR-BI knockout female mice.

***The Legal Standard for Enablement***

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. See, e.g., *Amgen v. Hoechst Marion Roussell* 314 F.3d 1313 (Fed. Cir. 2003) and *Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); and *In re Stephens*, 529 F.2d 1343 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir.1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the

quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation ' must not be unduly extensive.' *In re Atlas Powder Co., v. E.I. DuPont De Nemours & Co.* , 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir.1984).

As noted in *Ex parte Jackson*, the test is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. See *Ex parte Jackson*, 217 USPQ 804, 807 (PTO Bd. App. 1982). The adequacy of a specification's description is not necessarily defeated by the need for some experimentation to determine the properties of a claimed product. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F3d 956, 965-966 63 USPQ2d 1609, 1614 (Fed. Cir. 2002). There is no requirement for examples.

***The Specification Complies with the Enablement Requirement***

As discussed above, the claims are based on the discovery of *the nexus between fertility, steroidal levels, and cholesterol levels* (see, for example, page 7, lines 21-22; page 13, lines 14-

15; page 49, lines 16-20; page 49, lines 21-24 and Example 7). Because of this established connection, the appellant is claiming any compound that alters lipoprotein, LDL, HDL, or cholesterol levels mediated by SR-BI for the purpose of inhibiting pregnancy or decreasing production of steroids in an individual having a steroidal overproduction disorder. One can readily identify patients to be treated. It should be noted that the class of patients does not overlap with the normal class of patients treated with drugs altering cholesterol and/or lipoprotein levels. Most of these individuals are older - in the case of women, cholesterol does not typically increase until after menopause.

The examples have been discussed above. The paper showing restoration of fertility by administration of a cholesterol lowering drug, probucal, also discussed above, provides further support for the claimed method. The mere fact that this data was obtained after the filing date of the application makes the data no less relevant for demonstrating enablement which is asserted in the application, where the paper uses methods and materials known and readily available at the time the application was filed. The role of SR-BI in fertility is clearly established by the examples in the specification, whether it is to be restored in the case of knockout animals with insufficient SR-BI, or inhibited in the case of administering inhibitors of SR-BI. The role of SR-BI in cholesteryl transport was known (see, page 10, lines 19-21).

The appellant respectfully asserts that one of skill in the art would understand from the specification which compounds to use, and how to derive appropriate doses with minimal routine experimentation to practice the claimed method and inhibit fertility or treat a disorder characterized by excessive steroidal production.

## (9) SUMMARY AND CONCLUSION

Because HDL is the only lipoprotein present in substantial amounts in the follicular fluid surrounding the developing oocyte in humans, based on the data in the examples, it is expected that changes in HDL and/or SR-BI in humans may disturb oocyte maturation or function, and thus contribute to infertility. The present application, and its analysis of SR-BI knockout mice, ties together fertility and cholesterol level. The direct correlation that exists between cholesterol/HDL and the existence of SR-BI, lies at the core of the claimed method. Many compounds that already exist for regulating cholesterol levels can be used to inhibit pregnancy, or decrease steroidal production *via*, for example, the modulation of SR-BI expression or activity. It would not require undue experimentation to identify these compounds, the patients to be treated, or what constitutes an effective amount. Moreover, one skilled in the art would have no difficulty in identifying the scope of the claimed method in view of the specification, the examples, and the knowledge available to those skilled in the art.

For the foregoing reasons, Appellant submits that the claims 1-9, 12, 15, 16, and 19-22 are patentable.

Respectfully submitted,

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## Claims Appendix: Claims On Appeal

1. (previously presented) A method for inhibiting pregnancy or decreasing production of steroids in a mammal comprising

administering a compound inhibiting uptake, binding or transport of cholesteryl ester by SR-BI in the mammal in an amount effective to inhibit pregnancy or to decrease production of steroids in disorders involving steroidal overproduction.

2. (previously presented) The method of claim 1 wherein the compound alters SR-BI expression in a tissue.

3. (original) The method of claim 1 wherein the compound alters binding of SR-BI to high density lipoprotein including cholesteryl ester or other lipoproteins.

4. (previously presented) The method of claim 2 wherein the compound decreases SR-BI expression in the tissue of the mammal.

5. (previously presented) The method of claim 2 wherein the compound increases SR-BI expression in the tissue of the mammal.

6. (previously presented) The method of claim 3 wherein the compound decreases SR-BI binding to lipoprotein or transfer of cholesteryl ester in the tissue of the mammal.

7. (previously presented) The method of claim 3 wherein the compound increases SR-BI binding to lipoprotein or transfer of cholesteryl ester in the tissue of the mammal.

8. (original) The method of claim 1 wherein the mammal is a female and the compound is administered in an amount effective to prevent normal reproductive function.

9. (previously presented) The method of claim 1 wherein the mammal has a disorder characterized by an overproduction of steroids.

10. (cancelled)

12. (original) The method of claim 1 wherein the mammal has a disorder which can be treated by decreasing production of steroids.

15. (original) The method of claim 1 wherein the compound differentially alters the activity of, or expression of, SR-BI in different tissues.

16. (original) The method of claim 11 wherein the compound increases SR-BI expression in reproductive tissues and decreases or does not increase SR-BI expression in liver.

19. (withdrawn) The method of claim 1 wherein the compound is an antibody to SR-BI.

20. (previously presented) The method of claim 1 wherein the compound is a drug that decreases production of steroids via selective binding to SR-BI.

21. (previously presented) The method of claim 20 wherein the compound decreases cholesterol levels to decrease steroid levels.

22. (previously presented) The method of claim 21 wherein the compound inhibits cholesterol transport.

## Evidence Appendix

1. Meittinen, *et al*., *J. Clin. Invest*. 108:1717-1722 (2001).

2. Burns and Matzuk, "Minireview: Genetic Models for the study of Gonadotropin Actions" Endocrinology 143(8):2823-2835 (2002).

3. Matzuk and Lomb, "Genetic dissection of mammalian fertility pathways" Nature Cell Biology & Nature Medicine Fertility Supplement (2002) online table.

4. ALESSE® (levonorgestrel and ethinyl estradiol tablets) product information

## Related Proceedings Appendix

This case was previously on appeal as Appeal No. 2004-1823. There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

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